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(54) **Salts of amlodipine.**

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(73) Proprietor: **Pfizer Limited, Ramsgate Road, Sandwich Kent CT13 9NJ(GB)**

(72) Inventor: **Davison,Edward, 45 Leicester Avenue Cliftoncille, Margate Kent(GB)**
Inventor: **Wells, James Ingram, Dr., 'Ridgeways' High Street Wingham, Canterbury Kent(GB)**

(74) Representative: **Bradbrook, Geoffrey William et al, PFIZER LIMITED Ramsgate Road, Sandwich Kent, CT13 9NJ(GB)**

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Description

The present invention relates to improved pharmaceutical salts of amlodipine and pharmaceutical compositions thereof.

The compound amlodipine (3-ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate) is a potent and long acting calcium channel blocker having utility as an anti-ischaemic and anti-hypertensive agent.

European patent application publication no. 89167 discloses several different pharmaceutically acceptable salt forms of amlodipine. In particular the pharmaceutically acceptable acid addition salts are said to be those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions such as the hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts. Of these salts the maleate is disclosed as being particularly preferred.

It has now unexpectedly been found that the benzene sulphonate salt (hereinafter referred to as the besylate salt) has a number of advantages over the known salts of amlodipine and, additionally has unexpectedly been found to have a unique combination of good formulation properties which make it particularly suitable for the preparation of pharmaceutical formulations of amlodipine.

Thus according to the present invention there is provided the besylate salt of amlodipine.

In a further aspect the invention provides a pharmaceutical composition of the besylate salt of amlodipine together with a pharmaceutically acceptable diluent or carrier.

The invention further provides a tablet formulation comprising the besylate salt of amlodipine in admixture with excipients. A preferred formulation includes the besylate salt, a compression aid such as microcrystalline cellulose, an additive to provide sheen to the tablet such as anhydrous dibasic calcium phosphate, a disintegrant such as sodium starch glycollate and a lubricant such as magnesium stearate.

In addition the invention provides a capsule formulation comprising the besylate salt of amlodipine in admixture with excipients. A preferred formulation includes the besylate salt, an inert diluent, a dried disintegrant and a lubricant as described above.

The invention further provides the besylate salt of amlodipine in sterile aqueous solution for parenteral administration. Preferably such solution contains from 10 to 40% by volume of propylene glycol and preferably also sufficient sodium chloride to avoid haemolysis, e.g. about 1% w/v.

The invention also provides the besylate salt of amlodipine for use in treating ischaemic heart disease, especially angina, or hypertension, in a human being.

The invention also provides a process for preparing the besylate salt of amlodipine by reacting amlodipine base with a solution of benzenesulphonic acid or its ammonium salt in an inert solvent and recovering the besylate salt of amlodipine.

The preferred inert solvent is industrial methylated spirit.

Although amlodipine is effective as the free base, in practice it is best administered in the form of a salt of a pharmaceutically acceptable acid. In order to be suitable for this purpose the pharmaceutically acceptable salt must satisfy the following four physiochemical criteria: (1) good solubility; (2) good stability; (3) non-hygroscopicity; (4) good processability for tablet formulation, etc.

It has been found that whilst many of the salts outlined above satisfy some of these criteria, none satisfy them all and even the preferred maleate, whilst exhibiting excellent solubility tends to break-down in solution after a few weeks. Consequently a range of pharmaceutically acceptable salts of amlodipine has been made and evaluated using these criteria:

1. Generally, it is known in the art that a good aqueous solubility is necessary for good bioavailability. Usually a solubility of greater than 1 mg ml^{-1} at pH 1-7.5 is sought although higher solubilities are required to formulate injections. In addition salts which provide solutions having a pH close to that of blood (7.4) are preferred because they are readily biocompatible and can easily be buffered to the required pH range without altering their solubility.

As can be seen from the following comparative data the besylate salt of amlodipine exhibits good solubility and saturated solution p lt characteristics, compared with other salts.

Table 1

Salt	Solubility mg ml^{-1}	pH at saturation
Benzene sulphonate (besylate)	4.6	6.6
Toluene sulphonate (tosylate)	0.9	5.9
Methane sulphonate (mesylate)	25	3.1
Succinate	4.4	4.9
Salicylate	1.0	7.0
Maleate	4.5	4.8
Acetate	50	6.6
Hydrochloride	50	3.5

2. Good stability in the solid state is very important for tablets and capsules, whilst good stability in solution is required for an aqueous injection.
In order to screen for chemical stability, each of the salts was blended with a powder vehicle and formed into tablets or capsules. In the case of tablets the vehicle comprised microcrystalline cellulose in 50:50 combination with anhydrous dibasic calcium phosphate. In the case of capsules the vehicle comprised mannitol in 4:1 combination with dried maize starch. These were then stored in sealed vials at 50 and 75 °C for up to three weeks. The drug and any breakdown products were extracted with methanol:chloroform (50:50) and separated on silica tlc plates using a variety of solvent systems.
The results were compared and the salts ranked according to the number and amount of breakdown products produced.
By comparing the results the following rank order emerges with besylate being the most stable salt and hydrochloride the least stable.

Salt	Stability
Besylate	most stable
Mesylate	↓
Tosylate	↓
Succinate	↓
Salicylate	↓
Maleate	↓
Acetate	↓
Hydrochloride	unstable

3. In order to provide stable formulations it is desirable to have a non-hygroscopic salt. In the solid state where drug content is high, absorbed films of moisture can act as a vector for hydrolysis and chemical breakdown. It is the hygroscopic nature of a drug or its salt which contributes to the free moisture which is normally responsible for instability.
Only the maleate, tosylate and besylate salts do not pick up any moisture when exposed to 75% relative humidity at 37°C for 24 hours. Even when exposed to 95% relative humidity at 30°C for 3 days both the besylate and maleate remain anhydrous whilst the tosylate formed the dihydrate salt. Therefore the besylate salt can be considered to be non-hygroscopic and thus provides stable formulations while minimising the risk of intrinsic chemical breakdown.
4. The final characteristic of an acceptable salt to be considered is the processability, i.e. the compression properties and also the ability not to stick or adhere to the tablet making machinery.
For high dose formulations, good compressibility is very important to make legant tablets. With lower dose tablets the need for good compressibility can be eliminated to a certain extent by the use of suitable

diluting excipients called compression aids. Microcrystalline cellulose is a commonly used compression aid. However whatever the dose the adhesion of the drug to the punches of the tablet machine must be avoided. When drug accumulates on the punch surfaces this causes the tablet surface to become pitted and therefore unacceptable. Also sticking of the drug in this way results in high ejection forces when removing the tablet from the machine. In practice it is possible to reduce sticking by wet-massing, careful selection of excipients and the use of high levels of anti-adherents, e.g. magnesium stearate. However selection of a salt with good anti-adhesion properties minimises these problems.

In order to compare the stickiness of the various salts of amlodipine the following procedure was carried out using conventional tablet making machinery: fifty tablets containing calcium sulphate dihydrate, microcrystalline cellulose and amlodipine besylate were made (47.5:47.5:5), the material sticking to the tablet punch was then extracted using methanol and the amount measured spectrometrically. This procedure was then repeated for runs of 100, 150, 200, 250 and 300 tablets. After each run the amount of material sticking to the tablet punch was measured after extraction with methanol. The values are plotted and an average value calculated from the slope of the line produced.

This same procedure was then repeated for each of the salts of amlodipine. The amount of amlodipine measured as sticking to the tablet punch is shown in Table 2 for each salt and relative to the maleate salt.

Table 2

Salt	Stickiness μg Amlodipine cm^{-2} $tablet^{-1}$	Relative to maleate
Mesylate	1.16	58%
Besylate	1.17	59%
Tosylate	1.95	98%
Maleate	1.98	100%
Free base	2.02	102%
Succinate	2.39	121%
Hydrochloride	2.51	127%
Salicylate	2.85	144%

Clearly the besylate has superior anti-adhesion properties to the maleate. Whilst the mesylate also shows good processability it tends to be isolated as the anhydride but this equilibrates to the monohydrate leading to variable composition after manufacture which makes it unacceptable for use in tablets.

Thus the besylate salt of amlodipine shows a unique combination of good solubility, good stability, non-hygroscopicity and good processability which makes it outstandingly suitable for the preparation of pharmaceutical formulations of amlodipine.

In order that the present invention be more readily understood, reference is now made to the following Examples.

Example 1

Preparation of Besylate salt of Amlodipine

Amlodipine base (65.6g, 0.161 mols) was slurried in industrial methylated spirit (326.4 ml) and cooled to 5°C. Benzenesulphonic acid (26.2g, 0.168 mols) was dissolved in industrial methylated spirit (65.6 ml) at 5°C and added to the slurry of the base. The resulting slurry was then granulated, filtered and washed with 2 volumes of industrial methylated spirit (65.6 ml). The damp solid was slurried at 5°C for 1hr in industrial methylated spirit (327.6 ml), filtered, washed with 2 volumes of industrial methylated spirit (65.6 ml) and dried under vacuum at 55°C for 24 hours. A yield of 76.5g (83.8%) was obtained with the following analysis.

Melting point 201.0°C.

Analysis %	C	H	N
Calc.	55.07	5.51	4.94
Found	54.91	5.46	4.93

Exampl 2

Formulation of Tablets Containing Besylate Salt of Amlodipine

Amlodipine besylate was blended with sodium starch glycollate and anhydrous dibasic calcium phosphate for 5 minutes. This mixture was then sieved, reblended and sieved again followed by blending with microcrystalline cellulose. The resultant mixture was then sieved again and blended for a further 10 minutes. Finally magnesium stearate was added and the whole mixture blended for 5 minutes. The blend was then pressed into tablets using conventional tablet making machinery.

This method was used to make tablets containing different concentrations of the amlodipine besylate salt as shown in Table 3.

Table 3: Tablet compositions

Besylate salt (mg)	Microcrystalline cellulose (mg)	Anhydrous dibasic calcium phosphate (mg)	Sodium starch glycollate (mg)	Magnesium stearate (mg)
1.736	63.514	31.750	2.00	1.00
3.472	62.028	31.500	2.00	1.00
6.944	124.056	63.000	4.00	2.00
13.889	248.111	126.000	8.00	4.00

Example 3

Formulation of Capsules Containing Besylate Salt of Amlodipine

Microcrystalline cellulose and dried maize starch were pre blended. The besylate salt of amlodipine was then mixed with some of this preblend and then sieved. The remainder of the preblend was then added and mixed for 10 minutes. This was then sieved again and mixed for a further 5 minutes.

This method was used to make mixtures containing different concentrations of the amlodipine besylate salt as shown in Table 4 and the mixtures were then filled into capsules of appropriate size.

Example 4

Formulation of Sterile Aqueous Solution of Besylate Salt of Amlodipine

Sodium chloride was dissolved in water for injection and propylene glycol was mixed with this solution. The besylate salt of amlodipine was added and, when it had dissolved, further water for injection was added to adjust the volume to give the desired concentration of amlodipine (1 mg/ml). The solution was then filtered through a sterilising filter and filled into suitable sterile containers, e.g. ampoules, for use in parenteral, e.g. intravenous, administration.

This method was used to prepare the formulations shown in Table 5.

Table 5: Sterile Aqueous Solutions

	(1)	(2)
Besylate salt of amlodipine	1.389 g	1.389 g
Sodium chloride	9.000 g	9.000 g
Propylene glycol	200.000 g	400.000 g
Water for injection	to 1 litre	to 1 litre

Table 4: Capsule compositions

Besylate salt (mg)	Microcrystallin cellulose (mg)	Dried maize starch (mg)	Magnesium stearate (mg)	Total capsule weight (mg)
1.736	38.014	10.00	0.250	50
3.472	76.028	20.00	0.500	100
6.944	72.556	20.00	0.500	100
13.889	145.111	40.00	1.00	200

Example 5

Alternative preparation of Besylate salt of Amlodipine

Ammonium benzenesulphonate (0.943g) was added to a slurry of amlodipine base (2g) in industrial methylated spirit (10ml) and the resulting solution was heated at reflux for 10 minutes. The reaction mixture was cooled and granulated at 5°C for 1 hour. The amlodipine benzenesulphonate was filtered, washed with industrial methylated spirit (2 x 2 ml) and dried in vacuum.
Yield 1.9g (70% of theory).
Mpt.: 201.0°C.

Analysis %: –	C	H	N
Found:	54.98	5.46	4.90
Calculated for:	55.07	5.51	4.95

Claims for the Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. The besylate salt of amlodipine.
2. A pharmaceutical composition comprising the besylate salt of amlodipine as claimed in claim 1 together with a pharmaceutically acceptable diluent or carrier.
3. A tablet formulation comprising the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.
4. A tablet formulation as claimed in claim 3 wherein the excipients comprise a compression aid, an additive to provide sheen to the tablet, a disintegrant and a lubricant.
5. A tablet formulation as claimed in claim 4 wherein the excipients comprise microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycollate and magnesium stearate.
6. A capsule formulation comprising the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.
7. A capsule formulation as claimed in claim 6 wherein the excipients comprise an inert diluent, a dried disintegrant and a lubricant.
8. A capsule formulation as claimed in claim 1 wherein the excipients comprise microcrystalline cellulose, dried maize starch and magnesium stearate.
9. A sterile aqueous solution comprising the besylate salt of amlodipine for parenteral administration.
10. A sterile aqueous solution as claimed in claim 9 comprising from 10 to 40% w/v of propylene glycol.
11. A sterile aqueous solution as claimed in claim 9 or claim 10 comprising about 1% w/v sodium chloride.
12. The besylate salt of amlodipine for use in treating heart disease or hypertension.

Claims for the Contracting States: AT, ES, GR

1. A process for preparing the besylate salt of amlodipine characterised by the steps of reacting amlodipine base with a solution of benzenesulphonic acid or its ammonium salt in an inert solvent and recovering the besylate salt of amlodipine.
2. A process as claimed in claim 1 wherein the inert solvent is industrial methylated spirit.
3. A process for preparing a pharmaceutical composition characterised by the step of mixing the besylate salt of amlodipine with a pharmaceutically acceptable diluent or carrier.
4. A process as claimed in claim 3 for preparing a tablet formulation characterised by the steps of mixing the besylate salt of amlodipine with excipients and pressing into tablets.
5. A process as claimed in claim 4 characterised by the steps of
(a) blending the besylate salt of amlodipine with sodium starch glycollate and anhydrous dibasic calci-

um phosphate;
(b) sieving, reblending and sieving;
(c) blending with microcrystalline cellulose;
(d) sieving and reblending;
(e) blending with magnesium stearate; and
(f) pressing into tablets.

6. A process as claimed in claim 3 for preparing a capsule formulation characterised by the steps of mixing the besylate salt of amlodipine with excipients and filling into capsules.

7. A process as claimed in claim 6 characterised by the steps of
(a) preblending microcrystalline cellulose and dried maize starch;
(b) mixing the besylate salt of amlodipine with some of the preblend and sieving;
(c) mixing in the remainder of the preblend, sieving and re-mixing; and
(d) filling the mixture into capsules.

8. A process as claimed in claim 3 for preparing a sterile aqueous solution of the besylate salt of amlodipine for parenteral administration characterised by the steps of forming a solution of the besylate salt of amlodipine in a sterile aqueous carrier.

9. A process as claimed in claim 8 characterised by the steps of
(a) dissolving the besylate salt of amlodipine in a sterile solution of sodium chloride in a mixture of water for injection and propylene glycol;
(b) adjusting the volume of the solution with further water for injection;
(c) filtering the solution through a sterilising filter; and
(d) filling the solution into sterile containers.

10. A process as claimed in claim 8 or claim 9 in which the solution contains from 20 to 40% w/v propylene glycol and about 1% w/v sodium chloride.

Patentansprüche für: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Besylatsalz von Amlodipin.

2. Pharmazeutische Zusammensetzung umfassend das Besylatsalz von Amlodipin, wie in Anspruch 1 beansprucht, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.

3. Tablettenformulierung umfassend das Besylatsalz von Amlodipin, wie in Anspruch 1 beansprucht, in Mischung mit Exzipienten.

4. Tablettenformulierung, wie in Anspruch 3 beansprucht, worin die Exzipienten einen Preßhilfsstoff, ein Additiv zum Vorsehen von Tablettenglanz, ein Desintegriermittel und ein Gleitmittel umfassen.

5. Tablettenformulierung, wie in Anspruch 4 beansprucht, worin die Exzipienten mikrokristalline Zellulose, wasserfreies dibasisches Kalziumphosphat, Natriumstärkeglykolat und Magnesiumstearat umfassen.

6. Kapselformulierung umfassend das Besylatsalz von Amlodipin, wie in Anspruch 1 beansprucht, in Mischung mit Exzipienten.

7. Kapselformulierung, wie in Anspruch 6 beansprucht, worin die Exzipienten ein inertes Verdünnungsmittel, ein getrocknetes Desintegriermittel und ein Gleitmittel umfassen.

8. Kapselformulierung, wie in Anspruch 1 beansprucht, worin die Exzipienten mikrokristalline Zellulose, getrocknete Maisstärke und Magnesiumstearat umfassen.

9. Sterile wässerige Lösung umfassend das Besylatsalz von Amlodipin für parenterale Verabreichung.

10. Sterile wässerige Lösung, wie in Anspruch 9 beansprucht, umfassend 10 bis 40% G/V Propylenglykol.

11. Sterile wässerige Lösung, wie in Anspruch 9 oder 10 beansprucht, umfassend etwa 1% G/V Natriumchlorid.

12. Besylatsalz von Amlodipin zur Verwendung bei der Behandlung von Herzerkrankung oder Hypertonie.

Patentansprüche für: AT, ES, GR

1. Verfahren zur Herstellung des Besylatsalzes von Amlodipin, gekennzeichnet durch die Schritte des Umsetzens von Amlodipinbase mit einer Lösung von Benzolsulfonsäure oder ihres Ammoniumsalzes in einem inerten Lösungsmittel und Gewinnen des Besylatsalzes von Amlodipin.

2. Verfahren, wie in Anspruch 1 beansprucht, worin das inerte Lösungsmittel Industriemethylspiritus ist.

3. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, gekennzeichnet durch den Schritt des Mischens des Besylatsalzes von Amlodipin mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.

4. Verfahren, wie in Anspruch 3 beansprucht, zur Herstellung einer Tablettenformulierung, gekennzeichnet durch die Schritte des Mischens des Besylatsalzes von Amlodipin mit Exzipienten und des Verpressens zu Tabletten.

5. Verfahren, wie in Anspruch 4 beansprucht, gekennzeichnet durch die Schritte des
(a) Mischens des Besylatsalzes von Amlodipin mit Natriumstärkeglykolat und wasserfreiem dibasischem Kalziumphosphat,
(b) Siebens, neuerlichen Mischens und Siebens,
(c) Mischens mit mikrokristalliner Zellulose,
(d) Siebens und neuerlichen Mischens,
(e) Mischens mit Magnesiumstearat und
(f) Verpressens zu Tabletten.

6. Verfahren, wie in Anspruch 3 beansprucht, zur Herstellung einer Kapselformulierung, gekennzeichnet, durch die Schritte des Mischens des Besylatsalzes von Amlodipin mit Exzipienten und des Füllens in Kapseln.

7. Verfahren, wie in Anspruch 6 beansprucht, gekennzeichnet durch die Schritte des
(a) Vormischens von mikrokristalliner Zellulose und getrockneter Maisstärke,
(b) Mischens des Besylatsalzes von Amlodipin mit einem Teil der Vormischung und Siebens,
(c) Einmischens des Restes der Vormischung, Siebens und neuerlichen Mischens und
(d) Füllens der Mischung in Kapseln.

8. Verfahren, wie in Anspruch 3 beansprucht, zur Herstellung einer sterilen wässerigen Lösung des Besylatsalzes von Amlodipin für parenterale Verabreichung, gekennzeichnet durch den Schritt des Bildens einer Lösung des Besylatsalzes von Amlodipin in einem sterilen wässerigen Träger.

9. Verfahren, wie in Anspruch 8 beansprucht, gekennzeichnet durch die Schritte des
(a) Lösens des Besylatsalzes von Amlodipin in einer sterilen Lösung von Natriumchlorid in einer Mischung von Wasser für Injektionszwecke und Propylenglykol,
(b) Einstellens des Volumens der Lösung mit weiterem Wasser für Injektionszwecke,
(c) Filtrierens der Lösung durch einen Sterilisationsfilter und
(d) Füllens der Lösung in sterile Behälter.

10. Verfahren, wie in Anspruch 8 oder 9 beansprucht, wobei die Lösung 20 bis 40% G/V Propylenglykol und etwa 1% G/V Natriumchlorid enthält.

Revendications pour les Etats Contractants BE, CH, DE, FR, GB, IT, LU, NL, SE, LI

1. Le bésylate d'amlodipine.

2. Composition pharmaceutique, comprenant le bésylate d'amlodipine suivant la revendication 1, en association avec un diluant ou support pharmaceutiquement acceptable.

3. Formulation pour comprimés, comprenant le bésylate d'amlodipine suivant la revendication 1, en mélange avec des excipients.

4. Formulation pour comprimés suivant la revendication 3, dans laquelle les excipients consistent en un adjuvant de compression, un additif destiné à conférer un aspect luisant aux comprimés, un délitant et un lubrifiant.

5. Formulation pour comprimés suivant la revendication 4, dans laquelle les excipients consistent en cellulose microcristalline, phosphate monocalcique anhydre, glycolate d'amidon sodique et stéarate de magnésium.

6. Formulation pour capsules, comprenant le bésylate d'amlodipine suivant la revendication 1, en mélange avec des excipients.

7. Formulation pour capsules suivant la revendication 6, dans laquelle les excipients consistent en un diluant inerte, un délitant déshydraté et un lubrifiant.

8. Formulation pour capsules suivant la revendication 1, dans laquelle les excipients consistent en cellulose microcristalline, amidon de maïs déshydraté et stéarate de magnésium.

9. Solution aqueuse stérile, comprenant le bésylate d'amlodipine, destinée à l'administration par voie parentérale.

10. Solution aqueuse stérile suivant la revendication 9, comprenant 10 à 40% en poids/volume de propylèneglycol.

11. Solution aqueuse stérile suivant la revendication 9 ou la revendication 10, comprenant environ 1% en poids/volume de chlorure de sodium.

12. Bésylate d'amlodipine destiné à être utilisé dans le traitement d'une maladie cardiaque ou de l'hypertension.

Revendications pour les Etats Contractants AT, ES, GR

1. Procédé de préparation du bésylate d'amlodipine, caractérisé en ce qu'il comprend les étapes consistant à faire réagir l'amlodipine-base avec une solution d'acide benzènesulfonique ou de son sel d'ammonium dans un solvant inerte et à recueillir le bésylate d'amlodipine.

2. Procédé suivant la revendication 1, dans lequel le solvant inerte est l'alcool dénaturé.

3. Procédé de préparation d'une composition pharmaceutique, caractérisé en ce qu'il comprend l'étape consistant à mélanger le bésylate d'amlodipine à un diluant ou support pharmaceutiquement acceptable.

4. Procédé suivant la revendication 3 destiné à la préparation d'une formulation pour comprimés, caractérisé en ce qu'il comprend les étapes consistant à mélanger le bésylate d'amlodipine à des excipients et à effectuer la mise sous forme de comprimés.

5. Procédé suivant la revendication 4, caractérisé en ce qu'il comprend le étapes consistant

(a) à mélanger le bésylate d'amlodipine à du glycolate d'amidon sodique et à du phosphate monocalcique anhydre;

(b) à tamiser, à mélanger à nouveau et à tamiser;

(c) à effectuer un mélange avec de la cellulose microcristalline;

(d) à tamiser et à mélanger à nouveau;

(e) à effectuer un mélange avec du stéarate de magnésium; et

(f) à effectuer la mise sous forme de comprimés.

6. Procédé suivant la revendication 3, destiné à la préparation d'une formulation pour capsules, caractérisé en ce qu'il comprend les étapes consistant à mélanger le bésylate d'amlodipine à des excipients et à effectuer le remplissage de capsules.

7. Procédé suivant la revendication 6, caractérisé en ce qu'il comprend les étapes consistant

(a) à mélanger préalablement de la cellulose microcristalline et de l'amidon de maïs déshydraté;

(b) à mélanger le bésylate d'amlodipine à une partie du prémélange et à effectuer un tamisage;

(c) à effectuer le mélange au reste du prémélange, à tamiser et à mélanger à nouveau; et

(d) à remplir des capsules avec le mélange.

8. Procédé suivant la revendication 3, destiné à la préparation d'une solution aqueuse stérile du bésylate d'amlodipine pour l'administration parentérale, caractérisé en ce qu'il comprend les étapes consistant à former une solution du bésylate d'amlodipine dans un véhicule aqueux stérile.

9. Procédé suivant la revendication 8, caractérisé en ce qu'il comprend les étapes consistant

(a) à dissoudre le bésylate d'amlodipine, dans une solution stérile de chlorure de sodium, dans un mélange d'eau pour préparations injectables et de propylèneglycol;

(b) à ajuster le volume de la solution avec une quantité supplémentaire d'eau pour préparations injectables;

(c) à filtrer la solution à travers un filtre stérilisant; et

(d) à remplir des récipients stériles avec la solution.

10. Procédé suivant la revendication 8 ou la revendication 9, dans lequel la solution contient 20 à 40% en poids/volume de propylèneglycol et environ 1% en poids/volume de chlorure de sodium.